

09/485195

1 **Vinyl Sulphone Modified Polymer**2 a > Field of the Invention

3 The present invention concerns the preparation and use
4 of chemically functionalised polymeric resins for use
5 in solid-phase chemical synthesis.

6 a > Background of the Invention

7 Recent trends in the area of drug development,
8 biotechnology and chemical research have moved towards
9 producing large arrays of related molecules using
10 combinatorial or permutational synthesis. These
11 relatively new techniques are potentially capable of
12 yielding libraries of millions of compounds which can
13 be screened, if a suitable assay is available, to
14 identify the required chemical, physical or biological
15 property, ^{e.g.} biological activity. The new methods
16 offer advantage because only a relatively small number
17 of chemical reaction vessels need to be used, compared
18 to the traditional methods in which a single compound
19 is sequentially processed through various chemical
20 transformations, usually one reaction step at a time.
21 The new method, combinatorial synthesis, relies on the
22 fact that under suitable conditions and in the presence
23 of a single reagent or set of reagents, several to very
24 many compounds can be converted simultaneously into
25 several to very many new products using a singl

1 reaction vessel.

2

3 The problems with combinatorial chemistry are manifold.
4 First, the reaction chemistry needs to be irreversible,
5 such that each of the starting materials in the mixture
6 is converted to a new product in good yield. Second,
7 at the present time it is most feasible to perform
8 combinatorial chemistry in the "solid-phase", this is
9 where the starting materials are covalently bonded to a
10 polymeric support, usually cross-linked polystyrene.
11 The advantages of solid-phase synthesis are that the
12 products do not need to be purified by, for example,
13 solvent extraction, distillation, recrystallisation or
14 chromatography but rather are retained on the solid
15 medium by washing away the excess reagents and
16 impurities. Thus, in solid-phase synthesis it is
17 necessary to confine the polymeric support so that it
18 too is not washed away. The third problem concerns the
19 deconvolution of the library which essentially requires
20 identifying the chemical structure of the molecule,
21 within the mixture, that shows the required biological
22 activity or other desired property. Clearly, when one
23 is dealing with mixtures of compounds, where the
24 polymeric support for one compound looks identical to
25 that for another, one requires the resynthesis of
26 partial libraries of ever decreasing size, coupled with
27 assay, in order to identify the active material. This
28 method of deconvolution is time consuming and
29 unnecessarily clumsy. Another way of effecting
30 deconvolution is to tag the polymeric support with
31 chemicals which can be used to decode the synthetic
32 chemical history of the particular particle of
33 polymeric support, independently to being able to carry
34 out an activity assay on the material attached to the
35 support. Such methods have been described in the
36 literature. Since typical particles of polymeric

DRAFT PCT/GB98/02264

1 support are referred to as "resin beads" and are
2 commercially available in the size 70-400 microns,
3 deconvolution by such methods is a fiddly job requiring
4 accurate and expensive instrumentation.

5

6 The fourth problem concerns checking the efficiency of
7 the chemical synthesis and, in essence, this is a
8 problem of scale. Individual beads possess, at most,
9 only a few to several nanomoles of material attached to
10 them and, therefore, it is extremely difficult to check
11 either the efficiency of the synthesis or the purity of
12 the synthetic product. In highly sensitive biological
13 screening assays this can be a very serious problem as
14 the impurity could be responsible for a positive
15 result. The best way to overcome this last problem is
16 to perform syntheses on a larger scale such that some
17 material can be put aside for characterisation and
18 analysis. While this solution offers very many
19 advantages, the practice of a larger scale
20 combinatorial syntheses requires the design and use of
21 microreactors or other small individual reaction
22 chambers into which larger quantities of resin material
23 can be confined.

24

25 Small individual reaction chambers may be open or
26 closable flasks, tubes, 'pins', wells and other types
27 of standard laboratory apparatus. Microreactors may be
28 designed to contain resin beads within a porous
29 enclosure which is pervious to reagent solutions and
30 solvents.

31

32 Several reports on the use of microreactors for solid-
33 phase syntheses on a polymeric support, in which the
34 resin beads are enclosed within the microreactor, have
35 been described and include microreactors constructed
36 from polypropylene, which is not inert and

A

1 microreactors
2 microreactors construed from almost totally inert frit
3 ¹ glass and polytetrafluoroethylene. Other authors ¹ have
4 supplied little information on the design of the
5 microreactors or on how they were used in synthesising
6 libraries of compounds. The main purpose of the
7 reports was to describe the incorporation of an
8 addressable microchip into the microreactors which
9 could be written to and read using radio waves. This
10 elegant idea does require the microreactors to be of a
11 size large enough to contain the addressable chip and
12 also demands the use of sophisticated and moderately
13 expensive equipment.

14 The design and construction of visually addressable
15 microreactors for use in combinatorial chemical
16 synthesis is described in WO-A-97/30784. This
17 publication describes vessel designs suitable for use
18 with a whole range of different types of chemical
19 ^{environments} environment (due to the inertness of the microreactors)
20 ¹ and suitable for use with a whole range of different
21 types ¹ sizes and numbers of addressable microreactors.
22 The system was optimised for use with POSAM®
23 (Permutational Organic Synthesis in Addressable
24 Microreactors) where microreactor identification is
25 performed visually, but is also suitable for use with
26 radio-addressable microreactors or any other type of
27 microreactor tagging system or solid support tagging
28 system or hybrid tagging system ¹ including those which
29 utilise laser or mass spectrometric or radioisotope or
30 magnetic resonance or any other spectroscopic or
31 fluorimetric or related methodology which uses
32 electromagnetic radiation to detect the identity of, or
33 communicate with, the microreactor.
34
35 The stability of our previously described POSAM®
36 microreactors to the very wide range of reaction

1 conditions employed in conventional organic synthesis
2 is such that, in theory, almost every common synthetic
3 protocol described to date in the chemical literature
4 could be performed in the microreactor where all the
5 reagents are solutions, liquids or gases and can reach
6 the resin bound substrates (^{ie} the entities which are
7 being processed by the exposure to the reagents).

8 Obviously heterogeneous reagents and other particulate
9 matter above a certain size ~~can not~~ ^{cannot} pass through the
10 walls of the frit glass microreactors, and also
11 reagents which dissolve glass (hydrofluoric acid) or
12 react with PTFE (solvated electrons) are far from
13 ideal. Nevertheless, there is an enormous practical
14 potential for the use of POSAM® microreactors in
15 chemical synthesis which is currently limited by:

- 16 a) the stability of the polymer-base support used
17 in the commercially available resin materials that
18 are currently employed for solid-phase chemical
19 synthesis,
- 20 b) the range of functional groups available in
21 commercial resin materials. (For a comprehensive
22 list examples of available resin materials, see
23 the 1997 Nova solid-phase synthesis Catalogue).

24 ,
25 These two issues are not unrelated because some
26 functional groups would require such demanding
27 conditions to work with that the resin polymer base
28 would be destroyed under the required conditions.

29 The polymer base for almost all of the commercially
30 available resin materials, whether modified with
31 polyethylene glycol appendages to give Tentagel resins
32 or otherwise, is 1-2% divinylbenzene cross-linked
33 polystyrene in which approximately one in ten of the
34 phenyl rings derived from the styrene is modified to
35 give a benzyl moiety to which different functional

1 groups are attached. The chloromethyl (or benzyl
2 chloride) derivative is called Merrifield resin and
3 this material and its derivatives are mechanically
4 fragile and swell several fold in most organic solvents
5 (e.g. ^{e.g.} dimethylformamide, tetrahydrofuran,
6 dichloromethane) ^{e.g.}, but not all organic solvents (e.g.
7 methanol). The reaction kinetics for chemical
8 reactions performed on polystyrene-based resins is
9 drastically ^{affected} ^{e.g.} by how swollen the resin becomes
10 as it is solvated by the particular organic solvent.
11 Polystyrene is also chemically sensitive to some hot
12 organic solvents and is modified by solutions of the
13 very strong nucleophiles/bases and the protic and Lewis
14 acids commonly used in conventional synthesis.

15
16 Other polymer supports have found uses in biochemical
17 applications such as the preparation of affinity
18 columns for isolating and/or binding to proteins, DNA,
19 RNA, etc. These systems are usually used in aqueous
20 buffer solutions and the polymer support is usually
21 derived from polysaccharide, polyamide, polyacrylate or
22 polyacrylamide solid phases. These are, in general,
23 unsuitable for organic synthesis.

24 > Summary of the Invention

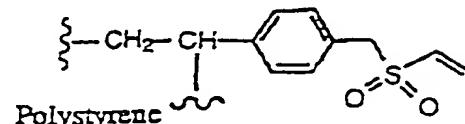
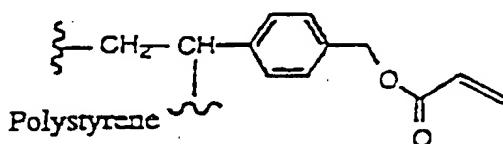
25 The present invention seeks to overcome disadvantages
26 associated with present practices in solid-phase
27 synthesis by providing new functional groups, to allow
28 a wider range of chemical manipulations and reactions
29 to be performed in solid-phase synthesis. The
30 synthetic steps could be performed in open vessels, for
31 example in standard laboratory flasks, in closed
32 vessels, for example in chromatography columns, or, in
33 microreactors where the resin material is contained
34 within a porous container. In particular, this
35 invention concerns the limitations of stability to
36 bases and nucleophiles in the acrylate ester REM resin

1 system that has been published in the literature.
 2 Detailed Description of the Invention

3 Specifically, the present invention provides a resin
 4 modified by vinyl sulphone moieties which support the
 5 same chemical reactivities as for the REM resin system
 6 and also serve as ^a "traceless linker" system, ^{while} ^{whilst}
 7 offering greater stability towards nucleophiles and
 8 bases and in particular towards unstabilised carbanions
 9 such as Grignard agents.

10

11 A summary of the REM system is given in Formula A
 12 below, whilst the vinyl sulphone system of the present
 13 invention is shown in Formula B.



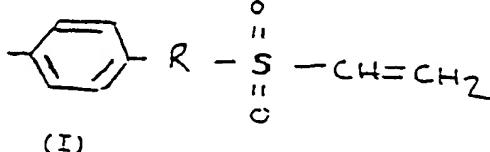
Vinyl Sulfone System

REM Resin System

A

20

21 The present invention provides ^a polymer having a side
 22 chain of general formula (I)



B

27 where R is an alkyl, aryl, oxyalkyl or oxyaryl linker
 28 group or any similar group.

29

30 Generally, the side chain will be attached to an
 31 ethylene moiety forming part of the backbone of the
 32 polymer.

33

34 The $\sim\text{CH}_2\text{-CH}\sim$ group is an ethylene grouping which is part
 35 of a resin backbone. Preferred resins include
 36 polystyrene.

1 The resin has increased stability in the presence of
2 nucleophiles and/or bases.

3

4 The resin particularly offers increased stability
5 towards unstabilised carbanions, for example, Grignard
6 reagents.

7

8 The vinyl group of the vinyl sulphone moiety may be
9 reacted with chosen reactants to provide resin-bound
10 compounds. Thus, the modified polymer is useful as a
11 support (resin) for solid phase chemical reactions,
12 especially combinatorial chemical synthesis.

13

14 The resin may be regenerated by the removal of the
15 resin-bound compounds by use of suitable reactants.

16

17 ~~Suitably, where R is an alkyl or oxyalkyl moiety, R is~~
18 ~~preferably a C₁₋₁₀ alkyl and may be branched or linear, and~~
19 ~~where R is an aryl or oxyaryl moiety, R is preferably a~~
20 ~~benzene ring or a group CH₂-O-Rhe-~~

21

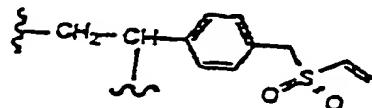
22 In one embodiment of the present invention, the
23 modified ethylene hydrocarbon polymer is a benzyl vinyl
24 sulphone polymer as represented by formula (II) in
25 which R is a -CH₂- group:

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27

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29



30

(II).

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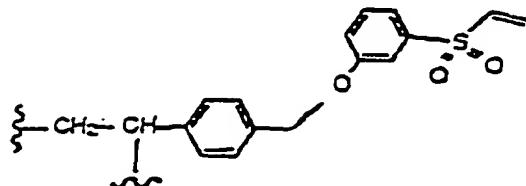
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35 In a further embodiment of the present invention, the
36 modified ethylene hydrocarbon polymer is a

1 benzyloxyaryl vinyl sulphone as represented by formula
2 (III):



10 The resin can be used in reactions involving liquid and
11 gas phase reactants.

12 Suitably, the resin is used for traceless reactions.

14

15 The resin has particular utility in solid-state
16 combinatorial chemical reactions.

17

18 Also provided by the present invention is a method for
19 producing the resin, wherein a Merrifield resin is
20 modified to provide the resin of the present invention;
21 for example, ~~but not limited to~~, the chlorine of the
22 methylene group of the Merrifield resin is substituted
23 to provide the resin of the present invention.

24

25 The present invention provides the use of the resin
26 defined above in the form of a porous structure as a
27 support for chemical reactions.

28 invention

29 The present ~~invention~~ will now be further described
30 with reference to the following, non-limiting,
31 examples.

32

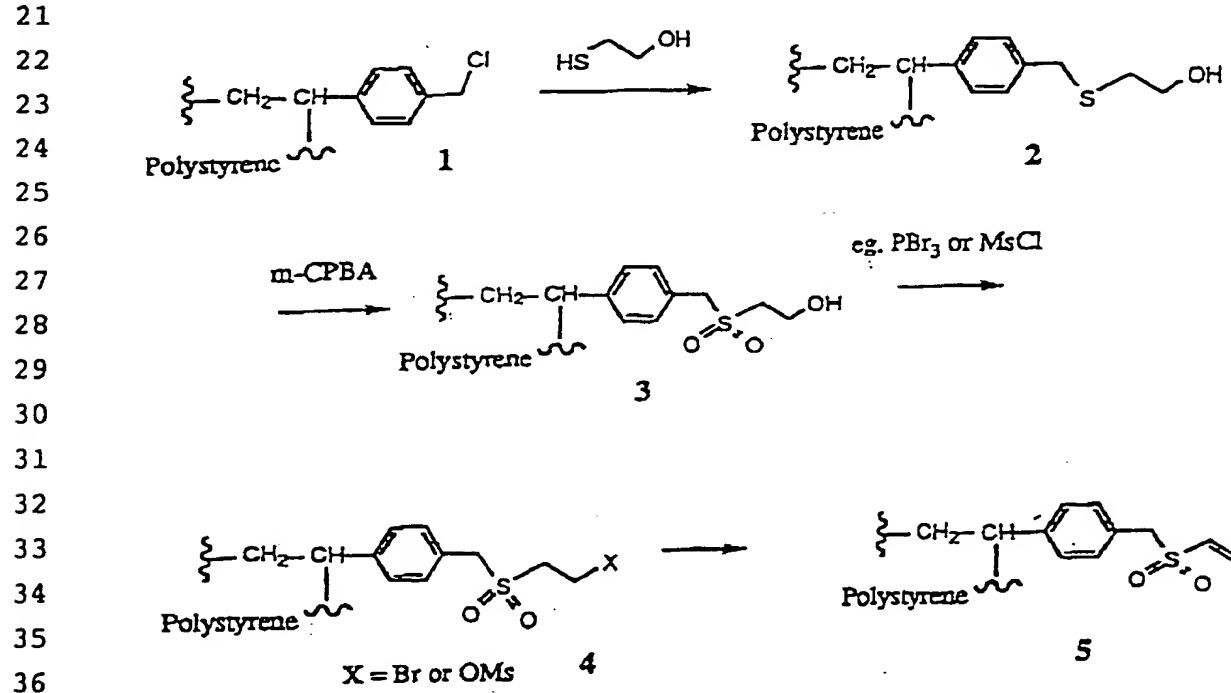
33 Example 1: Synthesis of polymer having a side chain of
34 formula II

35

36 With reference to the synthesis of the vinyl sulphone

1 system, a preferred process includes the steps
 2 summarised in Scheme 1 below in which Merrifield resin
 3 (1) was reacted with 2-hydroxyethylthiol ether as its
 4 sodium or caesium salt or as the free acid to give the
 5 thioether (2) which was subsequently oxidised with
 6 ozone or, preferably, *m*-chloroperoxybenzoic acid, to
 7 give the 2-hydroxyethylsulfone derivative (3). Each
 8 resin derivative showed the correct analytical data and
 9 displayed the expected spectral properties.

10
 11 Treatment of the resin (3) with phosphorous tribromide
 12 gave activated resin (4, X=Br) and then, after washing
 13 with dimethylformamide, treatment of this activated
 14 resin with a tertiary amine, for example,
 15 diisopropylethylamine (DIPEA), gave the resin bound
 16 polymer-benzyl vinyl sulfone (5). The same material
 17 (5) was obtained by treating resin (2) with methane
 18 sulfonyl chlorine in the presence of triethylamine, to
 19 give the mesyl activated ester (4, X=OMs) which
 20 underwent 1,2-elimination to give (5).



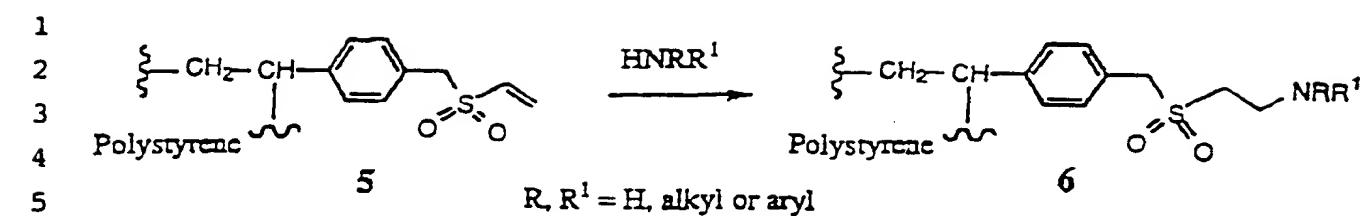
Scheme 1

1 Polymer-benzyl vinyl sulfone (5) could be either
2 trapped *in situ* or, be reacted separately, after
3 isolation, with a range of primary and secondary
4 amines. For example, reaction of secondary amine
5 tetrahydroisoquinoline (THIQ) for 8 hours at 25°C with
6 resin derivative (5) gave the resin bound tertiary
7 amine (6) which displayed the expected mass increase,
8 see Scheme 2. Similarly, diethylamine, benzylamine,
9 piperidine and pyrrolidine and/or their derivatives
10 gave the expected products which were characterised as
11 their alkylated derivatives as described below.

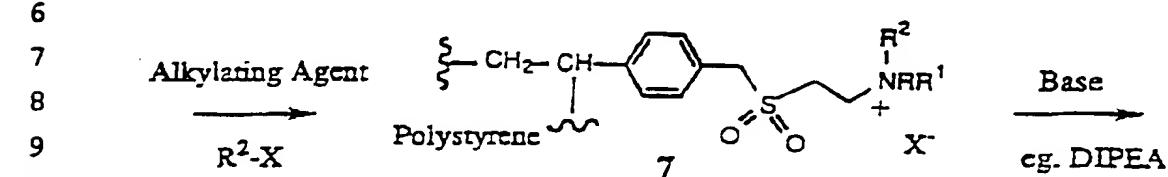
12
13 Treatment of resin bound tertiary amines such as (6)
14 with alkylating agents such as methyl iodide, benzyl
15 bromide or allyl bromide either at room temperature or
16 at higher temperatures gave the N-alkylated quaternary
17 ammonium salt derivatives (7). These could be cleaved
18 from the resin very conveniently by treatment of the
19 quaternary ammonium salt derivative with a mild base,
20 for example a tertiary amine such as triethylamine or
21 DIPEA, to give the required product, a new tertiary
22 amine (8) (as its salt) and to simultaneously
23 regenerate the resin bound polymer-benzyl vinyl sulfone
24 (5). In one instance, for example, the tertiary THIQ
25 amine derivative (6a) was formed from (5) and was
26 alkylated with allyl bromide to give the quaternary
27 ammonium salt (7a; R, R¹=THIQ, R²=allyl), which was
28 treated with DIPEA, to give
29 N-allyltetrahydroisoquinoline initially as its salt,
30 see Scheme 2 below.

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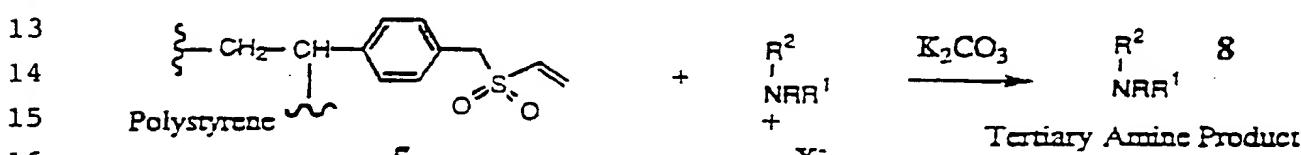
12



$R, R^1 = H, \text{alkyl or aryl}$



x = leaving group



Scheme 2.

in 6a and 7a $\text{NRR}' =$

The chemistry involving the addition of secondary amines to Michael acceptors to give a resin bound tertiary ^{amine} amines (cf. 6) or the construction of a tertiary amine by the Michael addition of a primary amine, followed by alkylation in the solid phase, is similar to that which occurs in the so called REM resin system which has been published in the literature. The REM system has a $\text{CH}_2\text{CHC=O}$ (acrylate) ester group in place of the vinyl sulfone of this new system (5). Furthermore, the alkylation of the resin bound tertiary amines followed by base-catalysed 1,2-elimination ^{i.e.} steps analogous to those for converting 6 to 7 and 7 to 5 in Scheme 2) have also been published in the literature for the REM resin system.

36 Note that for the REM resin system the entire sequence

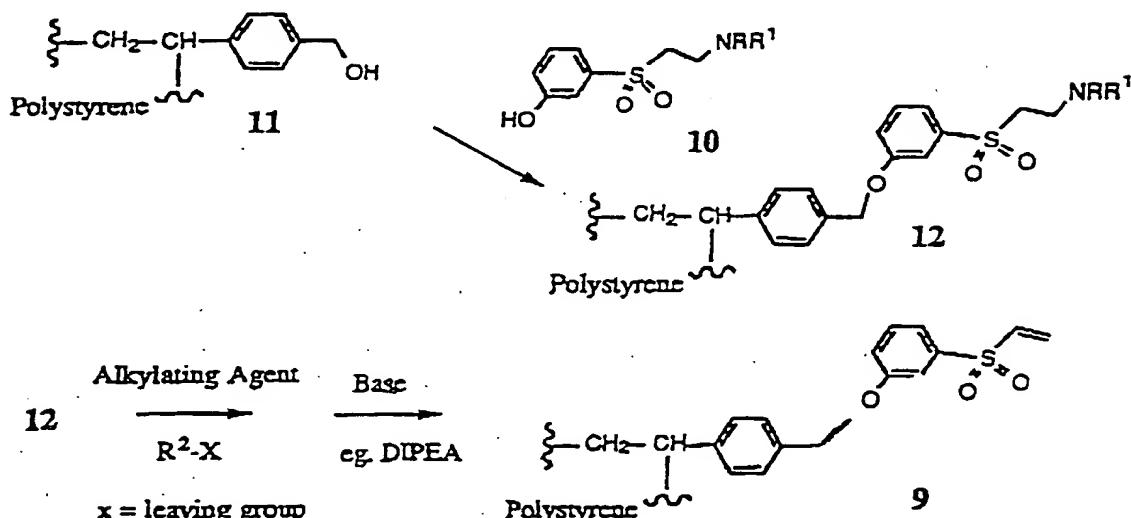
1 is analogous to the reported mechanism of action of the
2 enzyme methyl aspartase and related enzymes.

3

4 **Example 2: Synthesis of polymer having a side chain of**
5 **Formula III**

6

7 In a second embodiment of the invention, a Merrifield
8 derivative of the aryl sulphone system analogous to
9 resin (5), resin (9), was also prepared by reacting 3-
10 (N,N-dialkyl-2-aminoethylsulfonyl)-phenol (10) with
11 activated hydroxymethylpolystyrene resin (11) under
12 Mitsunobu conditions, and then alkylating and
13 eliminating the dialkylamino moiety, see Scheme 3,
14 using similar chemistry to that depicted in Scheme 2.
15 This gave a polymer benzyloxyaryl vinyl sulfone (9).



Scheme 3.

37 The resin also displayed all of the useful chemical
38 properties of REM resin, as for resin (5).

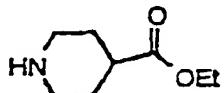
1 **Example 3: Solid phase reactive using vinyl sulphone**
 2 **polymers as solid-phase support**

3
 4 When tested in direct comparison with the REM resin
 5 system, both of the vinyl sulfone systems (5) and (9)
 6 showed very considerable advantages in stability in the
 7 presence of nucleophiles and bases. Indeed, it was
 8 possible to synthesise tertiary alcohols, for example,
 9 compounds (13) and (14) using the very demanding
 10 conditions of the Grignard reagents MeMgBr and PhMgBr .

11

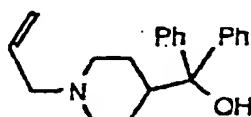
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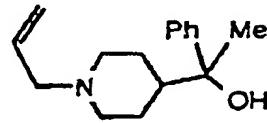


14

Ethyl Piperidine-4-carboxylate



(13)



(14)

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a For these examples, ethyl 4-piperidinecarboxylate (E4PC) ^{was} or the corresponding methyl ketone ^{were} first reacted with each of the vinyl sulphone resins to give the resin bound tertiary amines ^(e.g. 6, NRR'=E4PC), then ^{which} these were treated with the Grignard reagent PhMgBr to give the alcohols. The cleavage of these alcohols from the resin was effected using allyl bromide DIPEA as outlined in Scheme 2. Under these conditions, REM resin was completely decomposed by the Grignard reagents.

As was predicted, other addition reactions to the resin bound vinyl sulphones using non-nitrogen nucleophiles were also possible. For example, diethyl malonate, nitromethane and thiophenol reacted. Also, as predicted on the basis of solution phase chemistry, the resin bound vinyl sulphones (5) and/or (9), underwent Diels-Alder reactions and other electrocyclic reactions in the presence of dienes and/or 1,3-dipoles.

1 The range of addition and electrocyclic reactions in
2 which the resins (5) and (9) and other resin bound
3 vinyl sulphones could take part is infinite. *is included*
4 Therefore, within the spread of this invention *in any*
5 resin bound vinyl *sulphone* ¹ *moiety*, whether supported
6 on polymers or any similar *substituted* ¹ *ethylene*
7 hydrocarbon polymer, ^{and} ¹ in glass or silica or carbon
8 fibre, ^{whether} ¹ however linked to the support ⁱⁿ ¹ any synthetic
9 addition reaction or electrocyclic reaction, should be
10 considered as forming part of the invention described
11 herein.

12

13 **Example 4: Experimental Procedures for the use of**
14 **Vinyl Sulfone Chemistry on Polystyrene Resins**

15

16 Elemental microanalyses were performed in the
17 departmental microanalytical laboratory of the
18 University of St Andrews.

19

20 NMR spectra were recorded on a Bruker AM-300 (300 MHz;
21 f.t. ¹H-NMR, and 74.76 MHz ¹³C-NMR). Varian gemini 200
22 (200 MHz; f.t. ¹H-NMR and 50.31 MHz; ¹³C-NMR). ¹H-NMR
23 and ¹³C-NMR spectra are described in parts per million
24 downfield from TMS and are reported consecutively as
25 position (δ H or δ C), multiplicity (s-singlet, d-
26 doublet, t-triplet, q-quartet, dd-doublet of doublets,
27 ddt-doublet of doublets of triplets, m-multiplet and
28 br-broad), relative integral, coupling constant (Hz)
29 and assignment. ¹H-NMR are referenced internally on
30 CHCl₃, (7.25 ppm) or DMSO (2.47 ppm). ¹³C-NMR are
31 referenced on CHCl₃, (77.0 ppm), or DMSO (39.7 ppm).

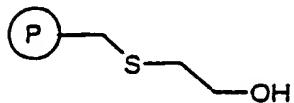
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33 IR spectra are recorded on a Perkin-Elmer 1710 f.t. IR
34 spectrometer. The samples were prepared as thin films
35 between sodium chloride discs or KBr disks (2%). The
36 frequencies (ν) as absorption maxima are given in

1 wavenumbers (cm^{-1}) relative to a polystyrene standard.
2 Intensities are reported as broad-br, strong-st, very
3 strong-vst, medium-m, weak-w. Mass spectra and
4 accurate mass measurements are recorded on VF 70-250
5 SE. Major fragments using the ^{ionization} ionisation method
6 indicated are given as percentages of the base peak
7 intensity (100%).

8
9 Abbreviations: DMSO, dimethylsulfoxide; DMF,
10 dimethylformamide; DCM, dichloromethane; THIQ,
11 tetrahydroisoquinoline; THF, tetrahydrofuran; mCPBA,
12 meta-chloroperoxybenzoic acid (Aldrich, 85%); DIPEA,
13 diisopropylethylamine; DEAD, diethylazodicarboxylate;
14 DIAD diisopropylazodicarboxylate; PE, petroleum ether
15 (fraction b.p. 40 -60°C); est., estimate;
16 max.est.yield, maximal estimated yield; (P), polystyrene.
17
18

2-Hydroxyethyl-thiomethyl - polystyrene 1



Method A: Merrifield resin (Novabiochem, 0.76 mmol g⁻¹, 5 g, 3.8 mmol) was suspended in dry DMF (40 cm³) and a solution of sodium 2-hydroxyethanethiolate, freshly prepared from NaH (12.5 mmol, 500 mg, 60% in mineral oil) and 2-hydroxyethanethiol (12.8 mmol, 0.9 cm³) in DMF (25 cm³), was added. The suspension was stirred at 60 °C for 4h then at 90 °C for 1h and then overnight at 20 °C. The resin was removed by filtration, washed successively with DMF, DCM, H₂O, DCM, MeOH / H₂O, DCM / DMF and with MeOH (50 cm³, each of them). The resin was dried under high vacuum with warming to 50 °C. Yield of resin 5.17 g. IR (ν_{max} / cm⁻¹, 2 % in KBr): 3500 (st), 3462 (br, OH), 1601, 1493, 1452 (st, polystyrene), 1059 (m), 1025 (m).

Sulfur analysis of 1: ~ 2.27 % (max. est. yield: 2.24 %)

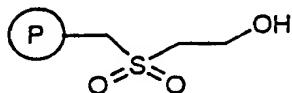
Method B: Merrifield resin (Novabiochem, 0.76 mmol g⁻¹, 3.8 g, 2.9 mmol) in dry DMF (20 cm³) was treated with 2-hydroxyethanethiol (15.25 mmol, 1 cm³), K₂CO₃ (14.5 mmol, 2 g) and pyridine (12.9 mmol, 1 cm³). The suspension was stirred for 4 h at 95 °C. It was left over night at 20 °C. The resin was filtered off and washed extensively with DMF, DCM, H₂O, H₂O / MeOH (1:1) and then pure MeOH and finally dried under high vacuum at 50 °C to give 3.92 g of material.

IR (ν_{max} / cm⁻¹, 2 % in KBr): 3450 (br, OH), 1601, 1493, 1453 (st, polystyrene), 1060 (m), 1027 (m).

Sulfur analysis: ~ 2.12 % (max: est. yield: 2.24 %)

Method C: Merrifield resin (Novabiochem, 0.76 mmol g⁻¹, 1.96 g, 1.45 mmol) in dry DMF (50 cm³) was treated with Cs₂CO₃ (2.98 mmol, 0.971 g) and 2-hydroxyethanethiol (14.96 mmol, 1.045 cm³). After stirring for 2 d at 20 °C the resin was drained and washed like in the cases A and B and dried at 45 °C under high vacuum. Yield: 1.86 g of resin.

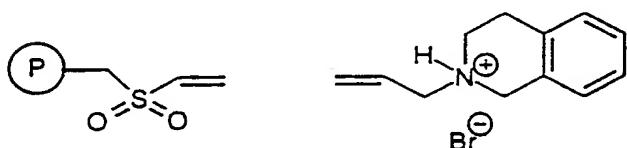
IR (ν_{max} / cm⁻¹, 2 % in KBr): 3425 (br, OH), 1601, 1493, 1453 (st, polystyrene), 1061 (m), 1029 (m).

2-Hydroxyethyl-sulfomethyl - polystyrene 2

Resin 1 (0.7 mmol g⁻¹ (est.), 1.5 g) were treated with mCPBA (5.2 mmol, 1.05 g). The suspension warmed up to 35 °C for a short period of time and was stirred at 20 °C for 2 d. After filtration the resin was washed with large quantities of MeOH, DCM, H₂O and MeOH, and dried at 50 °C under high vacuum. Yield: 1.51 g

IR (ν_{max} / cm⁻¹, 2 % in KBr): 3511 (br, OH), 1601, 1493, 1453 (st, polystyrene), 1317, 1119 (st, SO₂), 1061 (m), 1029 (m).

Sulfur analysis: ~ 2.76 % (max. est. yield: 2.19 %)

Vinylsulfomethylpolystyrene 3 and N-allyl tetrahydroisoquinoline HBr 4

Method A: resin 2 (0.65 mmol g⁻¹ (est.), 1.49 g) in dry DCM (25 cm³) were treated with PBr₃ (2.28 mmol, 216 mm³) at 20 °C for 12 h. The resin was filtered off, washed with DCM (200 cm³), dried at air and transferred to a flask with DMF (20 cm³) and THIQ (5.7 mmol, 725 mm³) was added. The resin was stirred at r. t. for 24 h, washed with DMF, MeOH, DCM, and MeOH. It was dried under high vacuum. 1.45 g (0.5 mmol g⁻¹ (est.)) of it was resuspended in DMF (10 cm³) and allyl bromide (150 mm³, 1.7 mmol) was added. After 5d at 20 °C the solid was filtered off, washed with DMF (100 cm³) and DCM (100 cm³). The resin was then treated with DIPEA (1.00 mmol, 175 mm³) in DCM (25 cm³). After 2 days the solid material was filtered off and washed with DCM and MeOH. Yield of resin 3 1.28 g (max. est. yield: 1.25 g). The solvent was removed from the filtrate and gave analytical pure 4 (0.47 mmol, 120 mg, 59 %) as a white solid.

3: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1727 (m), 1600, 1491, 1450 (st, polystyrene), 1320, 1119 (st, SO₂).

4: ¹H-NMR (δ / ppm, 300 MHz, CDCl₃): 12 (s, br, 1H, HBr), 7.30 - 7.08 (m, 4H, aromatics), 6.33 (ddt, 1H, $J^{\text{cis}}=10.0$ Hz, $J^{\text{trans}}=17.15$ Hz, $^3J=7.14$ Hz, CH₂-CH=CH₂), 5.61 - 5.5 (m, 2H, CH₂-CH=CH₂), 4.35 (br m, 2H, N-CH₂-Ph), 3.76 (d, 2H, $^3J=7.14$ Hz, CH₂-CH=CH₂), 3.42 (br m, 4H, N-CH₂-CH₂-Ph).

¹³C-NMR (δ / ppm, 74.76 MHz, CDCl₃): 130.54, 129.13 (2C, ⁷C), 128.78, 127.74, 127.05, 126.44, 126.38, 126.25 (remaining aromatics and double bond), 57.53 (N-CH₂-Ph), 51.43 (N-CH₂-CH=CH₂), 48.33 (N-CH₂-CH₂-Ph), 24.22 (N-CH₂-CH₂-Ph).

Found C, 56.57; H, 6.57; N, 5.42%. C₁₂H₁₆BrN requires C, 56.71; H, 6.34; N, 5.51%.

m/z (CI) 174 (M⁺ - Br⁻, 100%).

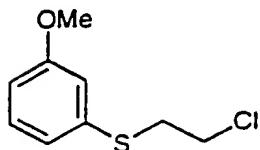
Method B: 2 (0.6 mmol g⁻¹ (est.), 0.57 g) in dry DCM (30 cm³) was treated with triethylamine (3.4 mmol, 4.78 mm³) followed by mesyl chloride (1.72 mmol, 133 mm³) at 20 °C. With addition the suspension became yellow and warms up slightly. It was stirred at ambient temperature for 12 h and the resin was filtered off, washed with DCM (200 cm³) and transferred into a sintered plastic tube with DMF (7 cm³). In the presents of THIQ (1.7 mmol, 216 mm³) the resin was agitated for 8 h, washed again with DMF and treated with allyl bromide (3.4 mmol, 300 mm³) in DMF (9 cm³). After 14 h at 20 °C the polymere was washed with DMF, MeOH and DCM. DIPEA (3.4 mmol, 600 mm³) in DCM (7 cm³) was added to the resin. After 12 h agitation the resin was washed with DCM and MeOH like under A and the solvent removed from the combined filtrates. The resin was dried at 50 °C in an oven under vacuum. Yield of resin 3: 0.55 g (max. est. yield: 0.51 g).

3: The amine 4 was liberated from its HBr salt with K₂CO₃ solution (2M, 10 cm³) extracted into EtOAc. The organic layer dried over K₂CO₃, filtered and the solvent removed. Yield of pure 4: 0.23 mmol, 40 mg, 68 %.

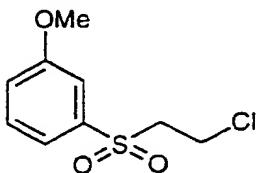
3: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1727 (m), 1600, 1491, 1449 (st, polystyrene), 1313, 1117 (st, SO₂), 1026 (m).

4: ¹H-NMR (δ / ppm, 300 MHz, CDCl₃): 7.14 - 7.01 (m, 4H, aromatics), 5.96 (ddt, 1H, J^{cis} = 9.9 Hz, J^{trans} = 17.15 Hz, ³J = 6.6 Hz, CH₂-CH=CH₂), 5.3 - 5.18 (m, 2H, CH₂-CH=CH₂), 3.63 (s, 2H, N-CH₂-Ph), 3.18 (dt, 2H, ³J = 6.5 Hz, ⁴J = 1.37 Hz, CH₂-CH=CH₂), 2.92 (t, 2H, ³J = 5.8 Hz, N-CH₂-CH₂-Ph), 2.75 (t, 2H, ³J = 5.8 Hz, N-CH₂-CH₂-Ph).

¹³C-NMR (δ / ppm, 74.4 MHz, CDCl₃): 135.28 (N-CH₂-CH=CH₂) (134.72, 134.26 (ipso carbons), 128.74, 126.64, 126.20, 125.65 (remaining aromatics), 118.03 (N-CH₂-CH=CH₂), 61.37 (N-CH₂-Ph), 55.88 (N-CH₂-CH=CH₂), 50.49 (N-CH₂-CH₂-Ph), 28.90 (N-CH₂-CH₂-Ph).

3-Methoxy-1-(2'-chloroethyl)thiophenol 5

N-Chlorosuccinimide (25.9 mmol, 2.86 g) was suspended in dry DCM (50 cm³). Slowly, 3-methoxythiophenol (25 mmol, 3.1 cm³) was added. After addition of 1 cm³ the suspension turned orange and warmed up. It was cooled for one minute with water and the remaining thiol was added in one go. The orange solution became clear and after 15 minutes a precipitate of succinimide ^{dropped} out of the solution. After ^{an} additional 15 minutes of stirring at 20 °C, the flask was filled with ethene. The suspension turned almost ^{colorless}, the solvent was removed and the residue stirred in carbon tetrachloride (50 cm³). Filtration and removal of the solvent gave crude 5 which was used in the following reaction. Crude yield of 5: 24.3 mmol, 4.93 g, 97%. 5: ¹H-NMR (δ / ppm, 200 MHz, CDCl₃): 7.29 - 7.21 (m, 1H, aromatic), 7.12 - 6.94 (m, 2H, aromatics), 6.93 - 6.75 (m, 1H, aromatics), 3.83 (s, 3H, OMe), 3.77 - 3.59 (m, 2H, -S-CH₂), 3.28 - 3.19 (m, 2H, Cl-CH₂).

3-Methoxy-1-(2'-chloroethyl)phenylsulfone 6

Crude 5 (24.2 mmol, 4.90 g) were dissolved in DCM (80 cm³) cooled to 0 °C and mCPBA (48 mmol, 9.7 g) were added in portions. The reaction was stirred over night and again treated with mCPBA (24.6 mmol, 5 g) in additional DCM (100 cm³). Ether (100 cm³) was used to dilute the suspension after 24 h and the organic layer was washed thoroughly with Na₂CO₃ solution (5 %, 100 cm³). Three washings with Na₂CO₃ (5 %), brine and drying over MgSO₄ followed. Yield of pure 6: 15.3 mmol, 3.58 g, 63 %, mp: 50.3 °C.

6: ¹H-NMR (δ / ppm, 200 MHz, CDCl₃): 7.52 - 7.35 (m, 3H, aromatics), 7.26 - 7.22 (m, 1H, aromatic), 3.89 (s, 3H, OMe), 3.80 - 3.72 (m, 2H, -SO₂-CH₂), 3.57 - 3.49 (m, 2H, Cl-CH₂).

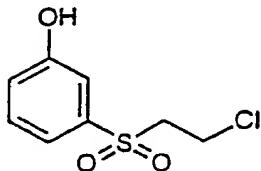
¹³C-NMR (δ / ppm, 74.76 MHz, CDCl₃): 160.42 (=COMe), 139.82 (=CSO₂), 130.83 (C⁵), 120.87 (C⁴), 120.33 (C⁶), 112.65 (C²), 58.02 (SO₂-CH₂), 55.81 (OCH₃), 35.57 (CH₂-Cl).

IR (ν_{max} / cm⁻¹, film): 1310, 1146 (st, SO₂), 1251, 1034 (Ph-O-Me).

21

Found C, 46.26%; H, 4.43%. $C_9H_{11}ClO_3S$ requires C, 46.06; H, 4.72%.
 m/z (CIHRMS) 235.020144 ($M^+ + H$, $C_9H_{12}ClO_3S$ requires 235.019569, 100%).

3-Hydroxy-1-(2'-chloroethyl)phenylsulfone 7



a To 6 (8.95 mmol, 2.1 g) in dry DCM (50 cm³) was added 1M BBr_3 (27 mmol, 27 cm³) in DCM at 0 °C. The solution was allowed to reach 20 °C ^{overnight} ^{overnight}, poured into ice water (100 cm³) and stirred for 1.5 h. The aqueous layer was saturated with NaCl and extracted with DCM. The combined organic layers were dried over $MgSO_4$. Filtration and removal of the solvent gave 7 as a white solid (7.8 mmol, 1.72 g, 87%). An analytical sample was obtained by recrystallisation from DCM (mp: 107.6 °C).

7: ¹H-NMR (δ / ppm, 300 MHz, $CDCl_3$): 7.51 - 7.41 (m, 3H, aromatics), 7.26 - 7.15 (m, 1H, aromatic), 6.10 (br s, 1H, OH), 3.77 - 3.72 (m, 2H, $-SO_2-CH_2$), 3.57 - 3.51 (m, 2H, $Cl-CH_2$).

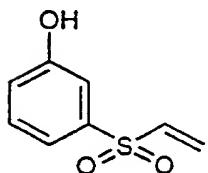
¹³C-NMR (δ / ppm, 50.31 MHz, $CDCl_3$ / (D_6)DMSO): 158.05 (=COH), 138.77 (=CSO₂), 130.18 (C⁵), 121.40 (C⁴), 118.04 (C⁶), 114.26 (C²), 57.39 (SO_2-CH_2), 35.29 (CH_2-Cl).

IR (ν_{max} / cm⁻¹, film): 3390 (s, OH), 1304, 1148 (st, SO₂).

Found C, 43.39; H, 3.78%. $C_8H_9ClO_3S$ requires C, 43.54; H, 4.11%.

m/z (CIHRMS) 221.004546 ($M^+ + H$, $C_8H_{10}ClO_3S$ requires 221.003919, 100%).

3-Hydroxy-1-phenylvinylsulfone 8



7 (7.3 mmol, 1.6 g) suspended in DCM (50 cm³) was slowly treated with DBU (10.9 mmol, 1.63 cm³) at 0 °C. After 10 minutes a second portion of DBU (3.3 mmol, 0.5 cm³) was added and the solution allowed to stir at 20 °C for 1.5 h. It was then poured into 2 % HCl (18 cm³) and Et_2O (150 cm³) was added. The organic layer was washed with 1M HCl (2 x 10 cm³) and brine, and dried over $MgSO_4$. After filtration and removal of the solvent the product was taken up in DCM and two ^{spoonfuls} of charcoal ^{were} added to the yellow solution. It was filtered ^{up}.

through a plug of silica, prewashed with PE / EtOAc (1:1). The filtrate was evaporated and ^{colorless} gave under high vacuum a ^{colorless} solid. Yield of 8: 6.25 mmol, 1.15 g, 86 %, mp: 58 - 60 °C.

8: ¹H-NMR (δ / ppm, 300 MHz, CDCl₃): 7.46 - 7.39 (m, 3H, aromatics), 7.16 - 7.11 (m, 1H, aromatic), 6.67 (dd, 1H, ^{trans}J = 16.5 Hz, ^{cis}J = 9.89 Hz, H^{gem}), 6.64 (d, 1H, ^{trans}J = 16.5 Hz, H^{cis}), 6.55 (s, 1H, OH), 6.07 (d, 1H, ^{cis}J = 9.89 Hz, H^{trans}).

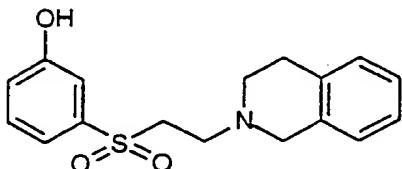
¹³C-NMR (δ / ppm, 50.31 MHz, CDCl₃): 157.53 (=COH), 140.22 (=CSO₂), 138.24 (SO₂-CH=CH₂), 131.38 (C⁵), 128.98 (SO₂-CH=CH₂), 122.06 (C⁴), 120.01 (C⁶), 114.87 (C²).

IR (ν_{max} / cm⁻¹, film): 3391 (st, OH), 1301, 1138 (st, SO₂).

Found C, 51.94; H, 4.40. C₈H₈O₃S requires C, 52.16; H, 4.38%.

m/z (EIHRMS) 184.019781 (M^+ , C₈H₈O₃S requires 184.019416, 100%).

3-Hydroxy-1-(2'-[N-tetrahydroisoquinoline]ethyl)phenylsulfone 9



8 (5.43 mmol, 1 g) in DCM (25 cm³) was treated dropwise with THIQ (6.25 mmol, 797 mm³) at room temperature. After 12 h precipitated 9 was filtered off as a white solid, washed with PE, and dried under high vacuum. Yield of 9: 5 mmol, 1.58 g, 92 %, mp: 177.0 °C.

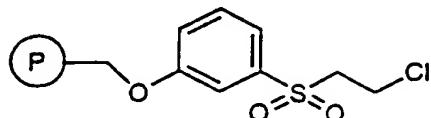
9: ¹H-NMR (δ / ppm, 300 MHz, (D₆)DMSO): 10.17 (s, 1H, OH), 7.43 - 7.25 (m, 3H, aromatics), 7.08 - 6.93 (m, 5H, aromatics), 3.55 (t (br), 2H, ³J = 7.14 Hz, -SO₂-CH₂), 3.48 (s, 2H, N-CH₂-Ph), 2.73 (t (br), 2H, ³J = 7.40 Hz, -SO₂-CH₂-CH₂-N), 2.66 - 2.55 (m (br), 4H, N-CH₂-CH₂-Ph).

¹³C-NMR (δ / ppm, 74.76 MHz, (D₆)DMSO): 158.44 (=COH), 141.13 (=CSO₂), 135.03 / 134.41 (C² / C⁶, THIQ), 131.11 (C⁵), 129.92 (C⁴, THIQ), 126.84 (C⁵, THIQ), 126.51 (C⁶, THIQ), 121.20 (C⁴), 120.0 (C³, THIQ), 118.56 (C⁶), 114.47 (C²), 55.28 (SO₂-CH₂), 52.79 (N-CH₂-Ph), 51.17 (-SO₂-CH₂-CH₂-N), 50.31 (N-CH₂-CH₂-Ph), 28.87 (N-CH₂-CH₂-Ph).

IR (ν_{max} / cm⁻¹, film): 3441 (st, OH), 1304, 1140 (st, SO₂).

Found C, 64.11; H, 6.19; N, 4.35. C₁₇H₁₉O₃NS requires C, 64.33; H, 6.03; N, 4.41%.

m/z (CIHRMS) 317.109012 (M^+ , C₁₇H₁₉O₃NS requires 317.108565, 100%).

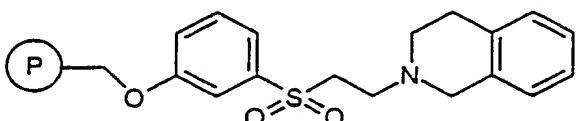
Methylene-3-oxy-1-(2'-chloroethyl)phenylsulfone polystyrene 10

To dry hydroxymethyl polystyrene resin (1.16 mmol g⁻¹, 431 mg) suspended in DCM / THF (1:1; 33 cm³), DEAD (2 mmol, 315 mm³) and 7 (4 mmol, 880 mg) were added. Triphenylphosphine (2 mmol, 524 mg) was added slowly, and the cleared suspension was stirred at 20 °C. After 3 h the resin was filtered off and washings with DCM / THF (1:1; 3 x 30 cm³), DCM (3 x 30 cm³), iPrOH (3 x 30 cm³) and MeOH followed. The resin was dried at 45 °C under vacuum. Yield 554 mg (max. est. yield: 550 mg).

The filtrate evaporated and chromatographed on silica (PE / EtOAc; 3:2) gave 7 (460 mg, 2.08 mmol) and 8 (129 mg, 0.7 mmol). The nmr was identical with authentic material.

10: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1600, 1493, 1453 (st, polystyrene), 1319, 1147 (st, SO₂), 1226 (st, -O-Ph).

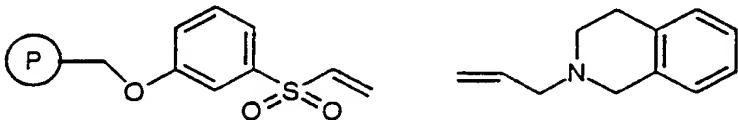
Sulfur analysis: 2.745 % (maximal possible yield: 3.71 %)

Methylene-3-oxy-1-phenylsulfone(2'-(N-tetrahydroisoquinoline)ethyl) polystyrene 11

To dry hydroxymethyl polystyrene resin (116 mmol g⁻¹, 431 mg) suspended in DCM / THF (1:1) (33 cm³), DIAD (2.5 mmol, 483 mm³), 9 (2.5 mmol, 790 mg) and triphenylphosphine (2.5 mmol, 655 mg) were added slowly. With the addition of triphenylphosphine the sulfone dissolved and the suspension ^{decolorized}. After 18 h the resin was filtered and washed with DCM / THF (1:1; 3 x 40 cm³), THF (50 cm³), DCM (50 cm³), MeOH, iPrOH, THF, DCM, iPrOH, and MeOH, and then again with DMSO, DMF, DCM and MeOH all 50 cm³. The resin was dried at 50 °C under vacuum. Yield 610 mg (max. est. yield: 580 mg).

11: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1600, 1493, 1453 (st, polystyrene), 1312, 1144 (st, SO₂), 1247 (st, -O-Ph).

Methylene-3-oxy-1-phenylvinylsulfone polystyrene 12 and N-allyl tetrahydroisoquinoline 4



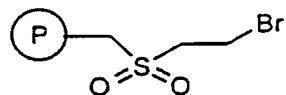
11 (0.97 mmol g⁻¹ (est.), 450 mg) in DMF (7 cm³) was treated with allyl bromide (8.75 mmol, 760 mm³) and agitated on a tube rotator for 15 h. The polymere was washed with several small portions of DMF, resuspended in DMF (7 cm³) and treated with methyl iodide (8.75 mmol, 545 mm³) and rotated under light protection for 6 h. The resin, washed with DCM, MeOH and DCM, was resuspended in DCM (7 cm³) and DIPEA (2.93 mmol, 510 mm³) added. The base ^{was} ^{decolorized} ^{decolourized} the material immediately. After 18 h shaking the resin was drained and washed with DCM and MeOH and dried under high vacuum in an oven at 50 °C. Yield of resin 12 401 mg (max. est. yield: 375 mg).

The filtrate was evaporated and gave 167 mg of white solid. It was treated with 2M K₂CO₃ (10 cm³) and extracted five times into DCM. The combined organic phases were washed with brine and dried over K₂CO₃. Filtration and removal of the solvent gave ^{colorless} 4 (0.28 mmol, 48 mg, 64 %) as an oil.

12: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1598, 1493, 1452 (st, polystyrene), 1312, 1141 (st, SO₂), 1222 (st, -O-Ph).

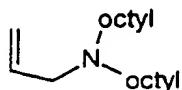
4: ¹H-NMR identical with an authentic sample.

2-Bromoethyl-sulfomethyl polystyrene 13



2 (0.6 mmol g⁻¹ (est.), 1.6 g) in dry DCM (25 cm³) was treated with PBr₃ (10.5 mmol, 1 cm³) and stirred slowly at r. t. for 24 h. The resin was filtered off, washed with DCM (100 cm³) and MeOH (100 cm³). Yield of resin 13 1.64 g (max. est. yield: 1.66 g).

13: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1601, 1493, 1453 (st, polystyrene), 1326, 1123 (st, SO₂), 1074, 1029 (st).

N-Allyl-N, N-di-n-octylamine 14

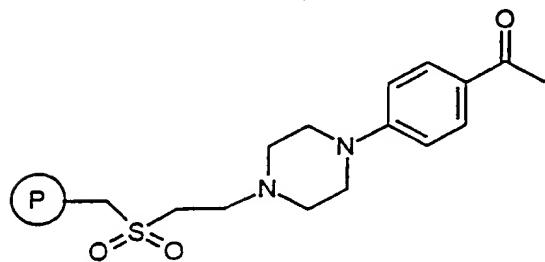
Resin 3 (0.42 mmol g⁻¹ (est.), 160 mg) in DMF (2 cm³) was treated with dioctylamine (1.7 mmol, 515 mm³) at 20 °C for 24 h. The resin was washed with DMF (10 x 5 cm³) and DCM (10 cm³), resuspended in DMF (2 cm³) and treated with allyl bromide (4.25 mmol, 365 mm³) at 20 °C for 24 h. The solvent and the reagent was then removed by filtration and the resin washed with DCM (2 x 20 cm³). The elimination was performed in DCM (4 cm³) with DIPEA (1.72 mmol, 300 mm³) ^{overnight}. The filtrate of this last reaction step was combined with the DCM and MeOH wash (25 cm³) from the resin and evaporated. It gave 14 contaminated with DIPEA in 38 mg yield. The amine was transferred in little DCM (< .5 cm³) to a K₂CO₃ covered dry silica column (5 g). Impurities were washed away with hexane and the amine eluted with ethyl acetate. After the removal of the solvent 14 (0.043 mmol, 12 mg, 64 %) was obtained as a colourless oil. It was contaminated with 5 % of 4 of a previous cycle.

IR of resin: identical to f.t. IR of resin 3.

14: ¹H-NMR (δ / ppm, 300 MHz, CDCl₃): 5.86 (ddt, 1H, ³J = 6.6 Hz, ³J^{cis} = 10.15 Hz, ³J^{trans} = 16.65 Hz, CH₂-CH=CH₂), 5.19 - 5.08 (m, 2H, CH₂-CH=CH₂), 3.08 (t br, 2H, ³J = 6.5 Hz, CH₂-CH=CH₂), 2.42 - 2.38 (m, 4H, 2 x N-CH₂-CH₂-), 1.47 - 1.26 (m, 24H, 2 x N-CH₂-(CH₂)₆-CH₃), 0.87 (t br, 6H, ³J = 6.73 Hz, N-CH₂-(CH₂)₆-CH₃).

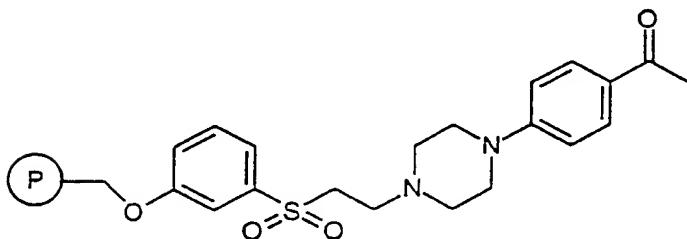
¹³C-NMR (δ / ppm, 74.76 MHz, CDCl₃): 136.34 (-HC=CH₂), 116.96 (-HC=CH₂), 57.33 (N-CH₂-CH=CH₂), 53.83 (N-CH₂-CH₂-), 31.82 (N-CH₂-CH₂-), 29.53 (N-(CH₂)₂-CH₂-), 29.27 (N-(CH₂)₃-CH₂-), 27.56 (N-(CH₂)₄-CH₂-), 26.87 (N-(CH₂)₅-CH₂-), 22.61 (N-(CH₂)₆-CH₂-), 14.02 (CH₃).

m/z (CIHRMS) 282.315253 (M⁺ + H, C₁₉H₄₀N requires 282.316076, 100%).

Sulfomethyl-2-(4'-piperazinoacetophenone)ethyl - polystyrene 15

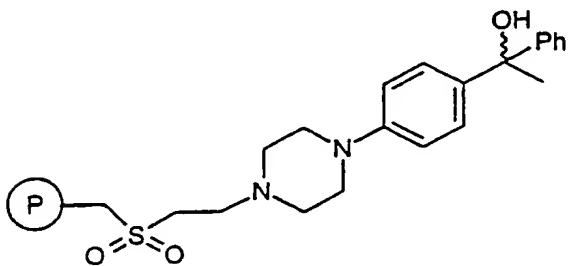
To 3 (0.36 mmol g⁻¹ (est.), 260 mg) in DMF (5 cm³) was added 4-piperazinoacetophenone (0.47 mmol, 95.6 mg) and agitated on a tube rotator for 24 h. The resin was drained, washed with DMF, DCM, and MeOH. Yield of resin 278 mg (max. est. yield: 279 mg).

16: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1651 (st, C=O), 1597, 1491, 1449 (st, polystyrene), 1305, 1114 (st, SO₂).

Methylene-3-oxy-1-[2'-(4"-piperazinoacetophenone)ethyl]phenylsulfone polystyrene 16

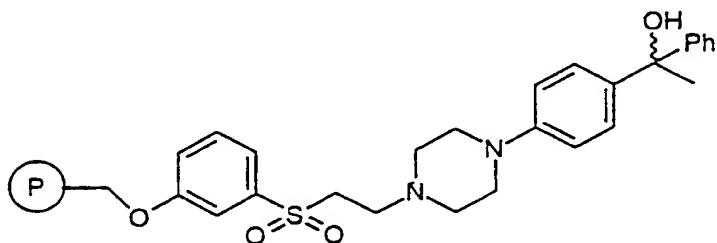
To 12 (0.51 mmol g⁻¹ (est.), 128 mg) in DMF (3 cm³) was added 4-piperazinoacetophenone (0.33 mmol, 67 mg). After 24 h the resin was washed with DMF and DCM and finally with MeOH. Yield 136 mg (max. est. yield: 141 mg).

17: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1664 (st, C=O), 1596, 1492, 1452 (st, polystyrene), 1310, 1139 (st, SO₂), 1230 (st, O-Ph).

Sulfomethyl-2-[4-piperazino-4-(α -methyl- α -phenyl-benzylalcohol)]ethyl - polystyrene 17

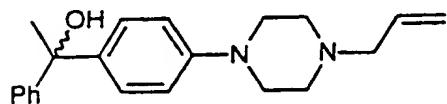
To 15 (0.36 mmol g⁻¹ (est.), 156 mg) in dry THF (5 cm³) was added 1M phenylmagnesium bromide in THF (390 mm³) at 0°C. After the addition the ice bath was removed and the reaction stirred for 2 h. It was quenched with 50 % aqueous NH₄Cl solution (5 cm³). The resin was washed four times with H₂O, THF, DCM, MeOH and dried at 50°C under vacuum. It gave 167.4 mg yellow resin (max. est. yield: 160 mg).

18: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3450 (vst, OH), 1600 (st, polystyrene), 1310, 1139 (st, SO₂).

Methylene-3-oxy-1-[2'-(4"-piperazino-4-(α -methyl- α -phenyl-benzylalcohol))ethyl] phenylsulfone polystyrene 18

16 (0.51 mmol g⁻¹ (est.), 106 mg) was treated in the same way like in the synthesis of 17 with 1M PhMgBr (530 mm³) in dry THF (5 cm³). Yield of resin 18 107.5 mg (max. est. yield: 110 mg).

19: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3420 (vst, OH), 1698, 1492, 1452 (st, polystyrene), 1306, 1140 (st, SO₂), 1223 (st, -O-Ph).

N-Allyl-4-piperazino-4-(α -methyl- α -phenyl-benzylalcohol) 19 from 17 and 18

To 17 (0.32 mmol g⁻¹ (est.), 160 mg) and 18 (0.5 mmol g⁻¹ (est.), 100 mg) were treated with allyl bromide (0.87 mmol, 75 mm³) (0.8 mmol, 70 mm³) in DMF (3 cm³ each) for 24 h. The resins were drained, washed with MeOH and DCM and resuspended in DCM (7 cm³). Treatment with DIPEA (0.57 mmol, 100 mm³) (0.5 mmol, 87 mm³) followed by agitation of the resins at 20 °C for 24 h ^{produced} gave after washings with DCM (15 cm³) and MeOH (10 cm³) the resins 3 and 12. The filtrates were evaporated and the HBr salt of the aminoalcohol 19 was obtained in both cases (8 mg and 12.6 mg respectively).

19 was further purified by applying the salt in DCM (< 0.5 cm³) to a dry silica column covered with K₂CO₃. Impurities were removed by hexane elution, the free amine 19 was eluted with 100 % EtOAc. Yield of 19 from 17 (9.3 μ mol, 3 mg, 16 %) and from 18 (17 μ mol, 5.5 mg, 35 %) (mp: 146 °C).

19: ¹H-NMR (δ / ppm, 300 MHz, CDCl₃): 7.42 - 7.20 (m, 7H, aromatics), 6.87 - 6.85 (m, 2H, aromatics), 5.90 (ddt, 1H, ³J = 6.59 Hz, ²J^{cis} = 10.20 Hz, ²J^{trans} = 16.80 Hz, CH₂-CH=CH₂), 5.25 - 5.16 (m, 2H, CH₂-CH=CH₂), 3.22 - 3.18 (m, 4H, 2 x N-CH₂-CH₂-), 3.05 (d, 2H, ³J = 6.59 Hz, CH₂-CH=CH₂), 2.61 - 2.52 (m, 4H, 2 x N-CH₂-CH₂-), 1.91 (s, 3H, CH₃).

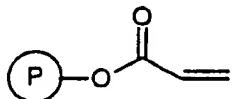
¹³C-NMR (δ / ppm, 74.76 MHz, CDCl₃): 150.23 (N-C=), 148.59 (ipso-phenyl), 139.16 (=C-C(CH₃)(OH)Ph), 134.79 (-HC=CH₂), 128.16, 126.94, 126.84, 125.99, 118.49 (remaining aromatics), 115.49 (-HC=CH₂), 76.96 (C-OH), 61.76 (N-CH₂-CH=CH₂), 53.01 (Tol-N-CH₂-CH₂-), 48.82 (Tol-N-CH₂-CH₂-N-allyl), 30.88 (HO-C(Tol)(Ph)CH₃).

IR (ν_{max} / cm⁻¹, 2 % in KBr): 3165 (m, OH), 1610, 1515, 1449 (st, =C-H), 1228 (st, N-C).

m/z (CIHRMS) 323.211904 ($M^+ + H$, C₂₁H₂₇ON₂ requires 323.212339, 85%); 305 ($M^+ + H - H_2O$, 100%).

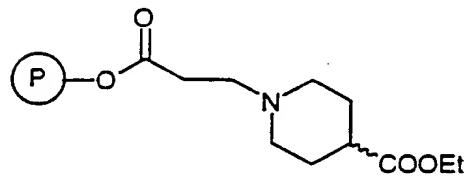
3: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3468 (st, OH), 1600, 1491, 1439 (st, polystyrene), 1315, 1120 (st, SO₂).

12: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3449 (st, OH), 1600 1493, 1453 (st, polystyrene), 1314, 1144 (st, SO₂), 1226 (-O-Ph).

REM resin 20

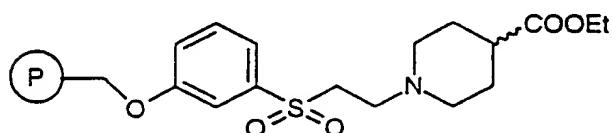
Hydroxymethyl polystyrene (0.8 mmol g⁻¹, 1 g) in dry DCM (10 cm³) was treated with DIPEA (6.9 mmol, 1.2 cm³) and acryloyl chloride (6.9 mmol, 560 mm³) at 20 °C. After 3 h the resin was filtered off and washed with DCM and MeOH thoroughly. After drying at 50 °C under vacuum ^a 1.08 g of resin 20 was obtained (max. est. yield: 1.015 g).

20: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3440 (vst, OH), 1720 (st, C=O), 1599, 1491, 1438 (st, polystyrene).

Carboxymethyl-2-(N-(ethyl isonipecotate))ethyl polystyrene 21

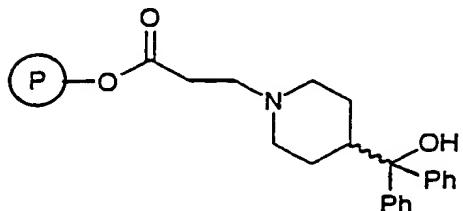
20 (0.77 mmol g⁻¹ (est.), 500 mg) in DMF (5 cm³) was treated with ethyl isonipecotate (3.85 mmol, 586 mm³) at 20 °C ^a overnight. The resin was then washed with DCM and MeOH and dried under vacuum at 50 °C. Yield ^a 546.5 mg (max. est. yield: 565 mg).

21: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3443 (vst, OH), 1735 (st, C=O), 1599, 1491, 1439 (st, polystyrene).

Methylene-3-oxy-1-[N-(2'-(ethyl isonipecotate)ethyl)]phenylsulfone polystyrene 22

12 (0.7 mmol g⁻¹ (est.), 300 mg) was treated with ethyl isonipecotate (3 mmol, 462 mm³) like in the synthesis of 21 and worked up in the same way. Yield ^a 333.5 mg (max. est. yield: 336 mg).

22: IR (ν_{max} / cm⁻¹, 2 % in KBr): 1736 (st, C=O), 1599, 1491, 1438 (st, polystyrene), 1315, 1145 (st, SO₂), 1249 (st, -O-Ph).

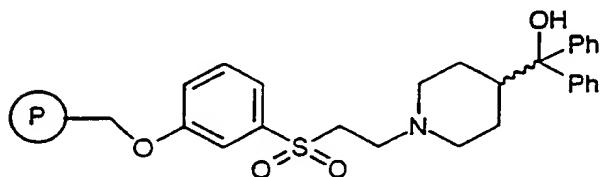
Carboxymethyl-2-[4-((α , α -diphenyl)methylalcohol)piperidine]ethyl polystyrene 23

To resin 21 (0.55 mmol g⁻¹ mmol (est.), 256 mg) in dry THF (10 cm³) was added 1 M PhMgBr in THF (840 mm³) with slow stirring at 0 °C. The ice bath was removed and the suspension stirred for 2 h at 20 °C. Addition of 50 % aqueous NH₄Cl solution (10 cm³) quenched the reaction and the resin was washed with water, THF, DCM and with MeOH.

After drying at 50 °C under vacuum, ^{the} yield of resin was 225 mg (max. est. yield: 271 mg).

23: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3448 (vst, OH), 1735 (w, C=O), 1598, 1491, 1438 (st, polystyrene).

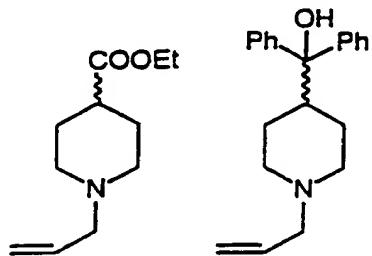
Methylene-3-oxy-1-[2'-(4-((α , α -diphenyl)methylalcohol)piperidine)ethyl]phenylsulfone polystyrene 24



22 (0.63 mmol g⁻¹ (est.), 159 mg) was treated in exactly the same way ^{like} 21 with 1M PhMgBr solution in THF (600 mm³). Yield of resin ¹⁶⁶ mg (max. est. yield: 170 mg).

24: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3448 (st, OH), 1596, 1508, 1438 (st, polystyrene), 1310, 1140 (st, SO₂), 1220 (st, -O-Ph).

Cleavage of N-allyl-ethyl isonipecotate 25 and N-allyl-4-((α,α -diphenyl)methylalcohol)-piperidine 26 from the resins 21, 22, 23, and 24



From the resins 21 - 24 the amines were cleaved in parallel experiments.

21 (0.55 mmol g⁻¹ (est.), 200 mg) was treated with allyl bromide (1.65 mmol, 143 mm³) in DMF (4 cm³) for 18 h on a tube rotator. The resin was washed with MeOH and DCM, resuspended in DCM (5 cm³) and treated with DIPEA (0.55 mmol, 96 mm³). After 24 h the resin was washed with DCM and MeOH. The combined filtrates were evaporated and along with the resin dried in an oven at 50 °C under vacuum.

Resins 22 (0.64 mmol g⁻¹ (est.), 164 mg), 23 (0.5 mmol g⁻¹ (est.), 215 mg) and 24 (0.59 mmol g⁻¹ (est.), 155 mg) were treated in the same way with allyl bromide (1.57 mmol, 136 mm³; 2.1 mmol, 181 mm³; and 1.5 mmol, 129 mm³ respectively) and with DIPEA (0.52 mmol, 91 mm³; 0.7 mmol, 122 mm³; and 0.5 mmol, 87 mm³ respectively).

21 gave 26 (49.6 mg) and resin 20 (188.5 mg).

22 gave 26 (36 mg) and resin 12 (188.5 mg).

23 gave 26 (11 mg) and resin 20 (188.5 mg).

24 gave 25 (25.6 mg) and resin 12 (133.7 mg).

The amines were transferred in little DCM (< 0.5 cm³) to a dry silica column topped with K₂CO₃. Impurities were removed by flushing the loaded columns with hexane. The free amines were obtained by ethyl acetate elution and removal of the solvent.

21 gave 26 (0.086 mmol, 16.9 mg, 78 %)

22 gave 26 (0.075 mmol, 14.7 mg, 71 %)

23 gave 26 (0.016 mmol, 3.2 mg, 20 % with regard to 21), 5 % of it was 25.

24 gave 25 (0.028 mmol, 8.6 mg, 42 % with regard to 22), 10 % of it was 26.

12: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3422 (st, OH), 1596, 1492, 1449 (st, polystyrene), 1309, 1139 (st, SO₂), 1220 (st, -O-Ph).

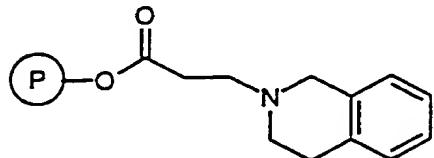
20: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3432 (vst, OH), 1719 (w, C=O), 1588, 1490, 1438 (st, polystyrene).

25: ¹H-NMR (δ / ppm, 300 MHz, CDCl₃): 5.86 (ddt, 1H, ³J = 6.59 Hz, ³J^{cis} = 10.15 Hz, ³J^{trans} = 17.10 Hz, CH₂-CH=CH₂), 5.2 - 5.10 (m, 2H, CH₂-CH=CH₂), 4.12 (q, 2H, ³J = 7.14 Hz, O-CH₂), 2.97 (dt, 2H, ³J = 6.6 Hz, ⁴J = 1.37 Hz, CH₂-CH=CH₂), 2.87 (dt, 2H, ³J = 3.44 Hz, ²J = 11.80 Hz, 2 x N-CHH-CH₂-), 2.26 (tt, 1H, ³J = 4.12 Hz, ³J = 11.00 Hz, EtOOC-CH), 2.05 (dt, 2H, ³J = 2.56 Hz, ²J = 11.50 Hz, 2 x N-CHH-CH₂-), 1.93 - 1.69 (m, 4H, N-CH₂-CH₂-), 1.24 (t, 3H, ³J = 7.01 Hz, O-CH₂-CH₃).

¹³C-NMR (δ / ppm, 74.76 MHz, CDCl₃): 175.31 (C=O), 135.39 (-HC=CH₂), 117.86 (-HC=CH₂), 62.03 (N-CH₂-CH=CH₂), 60.27 (O-CH₂-), 52.87 (N-CH₂-CH₂-), 41.00 (EtOOC-CH), 28.21 (N-CH₂-CH₂-), 14.14 (CH₃).

26: ¹H-NMR (δ / ppm, 300 MHz, CDCl₃): 7.49 - 7.45 (m, 4H, aromatics), 7.31 - 7.26 (m, 4H, aromatics), 7.20 - 7.14 (m, 2H, aromatics), 5.86 (ddt, 1H, ³J = 6.60 Hz, ³J^{cis} = 10.20 Hz, ³J^{trans} = 17.00 Hz, CH₂-CH=CH₂), 5.20 - 5.09 (m, 2H, CH₂-CH=CH₂), 2.98 (d, 2H, ³J = 6.90 Hz, CH₂-CH=CH₂), 2.97 - 2.88 (2H, m, 2xN-CHH), 2.47 - 2.38 (1H, m, HC-C(Ph)₂OH), 2.00 - 2.60 (m, 6H, 2 x N-CHH₂-CH₂-). This compound contains 10 % 25.

Carboxymethyl-2-(tetrahydroisoquinoline)ethyl polystyrene 27



27 was synthesised like 21 using resin 20 (0.77 mmol g⁻¹ (est.), 219 mg). Reaction resulted in 238 mg of resin (max. est. yield: 242 mg).

27: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3440 (st, OH), 1720 (st, C=O), 1599, 1491, 1438 (st, polystyrene).

Stability investigation of the resins 11 and 27

Treatment with 95 % TFA

11 (0.97 mmol g⁻¹ (est.), 65 mg) was treated for 2 h at 21 °C with 95 % aqueous TFA (3 cm³). The resin was drained and washed with DCM (10 cm³) and MeOH (10 cm³). The combined filtrates were evaporated at 45 °C. Yield of TFA salt of 2 (0.046 mmol, 20 mg, 73 %). It contained impurities.

27 (0.7 mmol g⁻¹ (est.), 70 mg) was treated in the same way and gave 5 mg of unidentified oil.³³

27: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3448 (st, OH), 1654 (m), 1600, 1491, 1425 (st, polystyrene).

11: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3456 (vst, OH), 1685 (st), 1599, 1508, 1449 (st, polystyrene), 1310, 1137 (w, SO₂), 1249.

2 from 11: ¹³C-NMR (δ / ppm, 74.76 MHz, (D₆)DMSO): 158.21 (=COH), 139.36 (=CSO₂), 135.03 / 134.41 (C² / C⁶, THIQ), 128.54 (C⁵), 127.68 (C⁴, THIQ), 126.61 (C⁵, THIQ), 126.42 (C⁶, THIQ), 121.20 (C⁴), 121.43 (C³, THIQ), 118.0 (C⁶), 113.99 (C²), 52.38 (SO₂-CH₂), 49.66 (N-CH₂-Ph), 49.23 (-SO₂-CH₂-CH₂-N), 48.43 (N-CH₂-CH₂-Ph), 25.15 (N-CH₂-CH₂-Ph).

Treatment with MeONa

To 27 (0.7 mmol g⁻¹ (est.), 50 mg) in THF (3 cm³) was added MeONa (0.75 mmol) in MeOH (300 mm³). After 3 h the resin was washed with MeOH and DCM and dried at 50 °C in a vacuum oven. Yield of resin 35 mg. The filtrate contained a methyl ester.

11 (0.97 mmol g⁻¹ (est.), 50 mg) was treated with the same amount of MeONa in MeOH in THF (3 cm³). It yielded 42 mg resin and 2 mg of an oil which did not contain a methoxygroup.

27: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3434 (vst, OH), 1631 (m), 1600, 1500, 1450 (st, polystyrene).

11: IR (ν_{max} / cm⁻¹, 2 % in KBr): 3450 (w, OH), 1598, 1500, 1451 (st, polystyrene), 1306, 1140 (st, SO₂), 1215.

¹H-NMR of the cleaved material from resin 27 shows in CD₃OD a methylester with OMe at 3.52 ppm and the expected aromatics from 7.85 to 7.182 ppm along with alkyl protones between 3.07 and 2.60 ppm.